PERIPHERAL NEUROPATHY WITH SEVERE INTRACTABLE HYponatremia AS A PRESENTATION OF ACUTE INTERMITTENT PORPHYRIA.

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ABSTRACT

Acute intermittent porphyria (AIP), the most common and the most severe form of acute hepatic porphyria, is an autosomal dominant condition. It results from lower-than-normal levels (less than 50%) of porphobilinogen (PBG) deaminase. Patients may present commonly with gastrointestinal complaints and neuropsychiatric manifestations. Diagnosis may be confirmed with the presence of intermediary metabolites of haem synthesis, Amino Levulinic Acid (ALA) and PBG in urine or with specific enzyme assays. Abdominal pain is the most common symptom (90%). Peripheral polyneuropathy, primarily motor with flaccid paresis of proximal musculature, with or without autonomic involvement, is characteristic. Respiratory failure necessitates mechanical ventilator and intensive care support. Avoidance of precipitating factors, the use of haem preparations and intravenous dextrose form the basis of management. Gabapentin and propofol, rather than the conventional antiepileptics appear to be the appropriate choice for seizure control.

We present a case of AIP who presented in porphyric crises, due to missed / delayed diagnosis and use of offending drugs, with peripheral neuropathy, respiratory paralysis and intractable hyponatremia with labile hypertension. Clinical presentation and issues pertaining to intensive care management of the case have been reviewed.

Keywords: Acute intermittent porphyria, intensive care management, porphobilinogen, respiratory failure

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CASE REPORT:

A 12 year old male child was admitted with chief complaints of oral ulcers, decreased oral intake for one week, confusion, inability to walk and inability to stand for one day.

He had a past history of admission to hospital on two occasions in the past four months. His first admission, being four months ago, was with history of fever, pain abdomen and recurrent generalised tonic clonic seizures. Consciousness was relatively preserved. MRI brain at that time revealed bilateral frontoparietal and occipital cortical hyperintensity on T2W images appearing iso and hypointense on T1W images with partial effacement of sulcal spaces. Child was treated with i.v antibiotics, acyclovir, sodium valproate, phenytoin sodium and resperidone.

Second admission was a month ago for chest pain, pain in legs, abnormal behaviour with head nodding, head banging and pulling out of lower incisors by the child. A lumbar puncture was done and CSF examination was normal at that time. MRI brain revealed resolving encephalitis. Child was continued on antiepileptic drugs, methyl prednisolone i.v. for 5 days and clobazam.

During this admission, he also had a history of poor sleep and constipation. On taking detailed history we were informed that child was born on term with normal vaginal delivery and had normal developmental history. School performance was normal prior to illness. There was no history of any contact with tuberculosis patient, seizures or chronic illness in the family.

On examination pulse rate was 130 per min, respiratory rate 24 per min, B.P 138/100 mmHg. Oral hygiene was poor with oral ulceration. Child had altered sensorium with low GCS (E4 V2 M1) .

There was hypotonia of both upper and lower limbs. Deep tendon reflexes were absent and plantars were indeterminate. Cranial nerves were normal. Motor power was 1-2/5 which progressed to 0/5 over next few days. Respiratory and cardiovascular systems were normal. Child was put on assisted ventilation after endotracheal intubation due to respiratory difficulty with respiratory muscle weakness on 5 th day of admission. A presumptive diagnosis of GBS, drug toxicity, encephalomyelitis was made.

On investigations child was anaemic with Hb of 8.8 gm/dl and WCC 10.2 x10^9/L with 70 % neutrophils, CSF examination was normal. Renal function and liver function tests were normal. Serum electrolytes revealed severe hyponatremia with serum sodium 108 meq/l and serum potassium 4.3 meq/l. Even after correction with 3% hypotonic sodium chloride, serum sodium levels ranged between 122 to 128 meq/l over next few days. Urinary sodium was 96 meq/l (N 40-220 meq/l). Serum levels of valproate and phenytoin were normal. Serum osmolality was 267 mosm/kg H2O and urine osmolality was >400-412 mosm/kg H2O. Colour of urine was noticed to be dark but urine examination did not show any abnormality. This prompted us to send urine for porphobilinogen which was positive, hence a diagnosis of AIP with acute crises was made.
Child had been started on i.v ampicillin, ceftriaxone, phenytoin, dexamethasone and ACE inhibitors on admission. Condition of child kept on deteriorating. After the diagnosis of AIP was clinched antiepileptic drugs, dexamethasone and ACE inhibitors were withdrawn and child was started on high carbohydrate diet (high concentration i.v dextrose) and propranolol to control B.P with continuation of antibiotics.

Child was continued on assisted ventilation for about 1 month. Due to prolonged need for ventilation tracheostomy was done after 10 days of intubation. During his stay child had fever with ventilator associated pneumonia. Weaning was gradually done after 1 month. Neurological improvement occurred with motor power improving to grade 3/5. Child was sent back home with tracheostomy tube with advice for follow up.

**DISCUSSION**

Acute porphyrias (AIP, hereditary coproporphyria, variegate porphyria and ALA dehydratase deficient porphyria) are characteristically hepatic porphyria, presenting with neurological manifestations. AIP usually presents with neuro-visceral and psychiatric disturbances like abdominal pain (90% of patients), constipation, insomnia, depression, disorientation, and hallucinations. In acute porphyric crisis, encephalopathy varying from confusion to frank psychosis can occur concomitantly with hypothalamic involvement and metabolic derangement of inappropriate secretions of ADH (anti-diuretic hormone). [2] Generalized seizures, myoclonic activity or coma may be observed due to neurological effects or hyponatremia. [3]

Polyneuropathy and painful flaccid paralysis predominantly involve upper limbs; preferentially affecting the proximal musculature with occasional sensory involvement. Motor weakness may be asymmetric and focal. Cranial nerves may be involved. Progressive muscle weakness can lead to life threatening respiratory and bulbar paralysis.

Autonomic disturbances may manifest as urinary retention, paralytic ileus, restlessness, tremors, excessive sweating, tachycardia and fluctuating blood pressure, typically labile hypertension. [4] Sometimes, persistent hypotension may require inotropic support. Complications like bradycardia and sudden cardiac arrest have also been reported. [1]

The reason for neurological involvement in acute porphyrias remains poorly understood. Direct neurotoxicity of delta-ALA by interaction with GABA receptor, altered tryptophan metabolism, or a neural respiratory haem-dependent enzymatic deficiency in nerve cells has been hypothesized. [5] Nevertheless, axonal degeneration of peripheral and autonomic nerve fibres rather than demyelination seems to be responsible. The neurological effects of acute porphyria are generally reversible, though incomplete recovery and residual paresis have also been reported. The reported mortality in porphyric polyneuropathy varies from 20-50%. [2] Sudden cardiac arrest secondary to autonomic dysfunction is known to cause death in these patients.
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Diagnosis of AIP requires a clinical suspicion with documentation of ALA and PBG in freshly voided urine. Classic burgundy red discoloration of long stored urine or Watson-Schwartz test using Ehrlich's aldehyde reagent are useful for screening. Quantitative measurements of PBG and ALA in urine or erythrocyte hydroxymethylbilane synthase enzyme test are more reliable confirmatory tests. These tests are suitable for screening asymptomatic family members, but, exorbitant cost limits their routine use. AIP at times mimic Guillain Barre Syndrome (GBS). [6] Absence of lymphocytosis with raised protein content in CSF favors a diagnosis of GBS rather than AIP.

Patients of AIP may require ventilatory support for progressive ascending paralysis with respiratory and/or bulbar muscle involvement. Varying neurological and mental dysfunction may necessitate treatment with analgesics, antiepileptics, and sedatives in addition to general care. During acute attacks, narcotic analgesics may be required for abdominal pain while phenothiazines may be useful for nausea, vomiting, anxiety and restlessness. Propofol has been tried successfully as a sedative [7] as well as an antiepileptic, [8] particularly in ITU settings. The primary AEDs such as phenytoin, barbiturates, carbamazepine, and sodium valproate are unsafe and better avoided, in patients with seizures. Magnesium sulfate is useful for emergency treatment of seizures, but, not for long-term use. Gabapentin appears to be a safe and effective alternative with a promising future. [9] It is not appreciably metabolized in the liver nor does it have any effect on hepatic microsomal enzymes.

Haem in the form of hematin (Abbott laboratories), haem albumin or haem arginate 3-4 mg/kg/day (Leiras Oy, Turku, Finland) infused daily for 3-4 days is the treatment of choice for AIP. [1] Haem acts by repressing the ALA synthetase enzyme and thus, further suppressing the production of haem precursors. Associated high cost and lack of availability are the main drawbacks. It was not used in our patients due to unavailability. Alternatively, carbohydrate rich diet is used. Intravenous dextrose in higher doses (300-500 gm/day) blocks induction of the enzyme and prevents accumulation of precursors. High-dose of dextrose may not only be used as a substitution; but also for providing a more complete parenteral nutritional regimen whenever oral feeding is delayed.

The most important step in preventing further crises is to withdraw the precipitating factors such as prolonged fasting, dehydration, stress, hypothermia, infection, and fever. Porphyrogenic drugs like barbiturate, antiepileptics (some), erythromycin, chloramphenicol etc. should be avoided. [1] These are inducers of hepatic metabolism thereby subjecting the patients to acute porphyric attacks. Hence, drugs not dependent on liver for metabolism should be preferred. Pregnancy, alcohol and female sex hormones are some other associated risk factors for acute crises.

To conclude, patients with AIP constitute a group of critically ill patients who require specialized care. High clinical suspicion, early diagnosis, and management of an acute attack along with measures to prevent future attacks
are the mainstay of a favorable outcome. AIP should always be suspected in the setting of neuro-psychiatric manifestations in patients with gastrointestinal complaints. Families of these individuals should be subjected to suitable enzyme tests, where facilities exist, to screen asymptomatic relatives.

REFERENCES